Meta-Analyses on Passive Smoking and Lung Cancer

H. Letzel and K. Überla

Summary

Up to now, meta-analysis has rarely been used in epidemiology and no generally accepted standards are available. Combining risk estimates from biased or confounded studies by meta-analysis cannot provide correct answers.

In our paper two cohort and ten case-control studies were analyzed using several statistical techniques (Fisher, Mantel-Haenszel, Yusuf). Only data from women were included and a quality indicator (histology exposure, methodology) was used to analyze different study combinations, i.e. an analysis of sensitivity was performed. For the Hirayama study two different risk estimates were used. In addition, all 1,023 logically possible combinations of the 10 case-control studies were analyzed.

Of all possible meta-analyses of the 10 case-control studies, 670 (65.5%) were not significant at $P \leqq 0.05$ (Yusuf technique). The Trichopoulos study is involved in 330 of the 353 significant study combinations, indicating that this is the dominating case-control study, although the methodological quality is unacceptable.

Combining case-control and cohort studies, the relative risk estimates range from 1.013 to 1.118, depending on the specific subset of studies analyzed. These relative risk estimates include unity. The quality of the individual studies is highly variable and sometimes poor. We conclude that as long as no better studies are available, meta-analyses cannot and do not add much new evidence to the question of whether passive smoking is related to lung cancer.

Up to now, meta-analyses have mainly been used with randomized clinical trials. The technique has been criticized [6, 10, 23] for various reasons. Standards for meta-analyses in epidemiology are not yet available. Bias by non-reporting of studies, by selecting certain subgroups or by redefining sample sizes can create additional difficulties for a statistical evaluation. How different study designs – e.g. case-control versus cohort studies – should be weighted is left to the investigator. It is not surprising that the application of such methods in a controversial field like passive smoking and lung cancer does not come up with uniform results.

The inclusion of studies in meta-analyses is justified as long as there are no major methodological shortcomings in the individual studies. Combining biased or confounded results by meta-analysis cannot provide correct answers. There is a strong case for an analysis of sensitivity [23]. It investigates the effect of different study selections as well as the impact of different statistical methods on the results.

When the first papers on passive smoking and lung cancer were published a serious hypothesis was created [11, 27]. This hypothesis is serious because – if it is right – thousands of non-smokers are being killed worldwide by smokers. But the hypothesis is also serious because – if it is wrong – smokers are being accused of killing other people without actually doing so.

H. Kasuga (Ed.) Indoor Air Quality

Last year Wald [31] published the first meta-analysis of the available studies on passive smoking and lung cancer. In his paper the results obtained in men were included, and in two studies the subgroup of women married to ex-smokers was excluded. The quality of the individual studies was not taken into account and no analysis of sensitivity was performed.

Every meta-analysis has to state its goals, criteria and methods before it starts. In our analysis we planned

1) to include only studies which fulfil minimal methodological requirements. We wanted to eliminate statistical noise.
2) to select carefully the "best" relative risk estimate from every study, not just the one which was reported by the authors or the highest one.
3) to classify the quality of the studies regarding determination of histology, estimation of exposure and overall study methodology.
4) to use different statistical techniques, namely the Fisher method and the method used by Yusuf [32] or Wald [31].
5) to study the sensitivity of the results with regard to including different subsets of studies depending on their qualities.

Selection of Studies

We did not include the studies by Gillis [9], Knoth [16], Miller [22] and Sandler [24–26]. These studies do not fulfil minimal methodological criteria and they do not contain relevant information. Only insufficient data are available from them. Wald [31] had included the Gillis study [9], which only has 14 non-smoking lung cancer cases and correspondingly wide confidence intervals contributing nothing to the available evidence.

We also excluded men because the majority of evidence comes from studies in women. Only about 11% of the reported cases are men. Their results vary widely. There is not a single significant result in men. The situation regarding biology, exposure and reporting habits is considerably different in men as compared to women.

We included two cohort studies [7, 12–14] and 10 case-control studies [1–5, 8, 15, 17, 19–21, 27, 28]. These studies had also been included by Wald [31]. The only difference is that we didn't include the Gillis study [9] and that we restricted our analysis to women. The availability of histology, the quality of the exposure indicator and an overall quality rating of the study were judged by K. Überla. Three study groups resulted: cohort studies, case-control studies with reasonable quality (quality +) and case-control studies with poor quality (quality −) (Table 1).

The 2×2 tables and RR estimates for the 12 studies used are presented in Table 2. Generally, these numbers are the same as used by Wald [31] with the exception that we did not exclude the wives of ex-smokers in the studies by Hirayama [14], Trichopoulos [27, 28] and Koo [17].

Regarding the Hirayama study we did not use a relative risk estimate of 1.63 as did Wald [31]. In a subsequent paper by Überla and Ahlborn [30], which will be presented in this session of the conference, it is shown that, when one adjusts the Hirayama cohort to the age of the female population in Japan, the relative risk is 0.90. We alternatively used a risk estimate of 1.45 for the Hirayama study. This was calculated from Table 2 of the 1984 publication by Hirayama [13] and was standardized by the age of women only.

Table 1. Quality rating of studies selected for meta-analyses

Author	Histology	Exposure	Quality rating**	Resulting group
Hirayama	−*	−	3	Cohort
Garfinkel	−	−	2	Cohort
Chan et al.	±	+	4	CC quality +
Correa et al.	−	±	5	CC quality −
Trichopoulos et al.	−	±	6	CC quality −
Buffler et al.	+	−	4	CC quality +
Kabat et al.	+	+	4	CC quality +
Garfinkel et al.	+	+	4	CC quality +
Akiba et al.	−	−	5	CC quality −
Lee et al.	−	+	5	CC quality −
Koo et al.	±	+	4	CC quality +
Pershagen et al.	+	+	4	CC quality +

The included studies are the same as in the paper by Wald et al. (1986). We included women only.
** 2 = acceptable; 3 = possibly flawed; 4 = bias and confounding suspected; 5 = major bias and confounding suspected; 6 = unacceptable

Table 2. 2 × 2 Tables and relative risk estimates for studies selected for meta-analyses

Author	Exposed lung cancer		Unexposed lung cancer		Relative risk
	+	−	+	−	
Hirayama	163	69,428	37	21,858	1.45 (1) 0.90 (2)
Garfinkel	88	127,164	65	49,422	1.18
Chan et al.	34	66	50	73	0.75
Correa et al.	14	61	8	72	2.03
Trichopoulos et al.	53	116	24	109	2.01
Buffler et al.	33	164	8	32	0.80
Kabath et al.	13	15	11	10	0.79
Garfinkel et al.	91	254	43	148	1.23
Akiba et al.	73	188	21	82	1.48
Lee et al.	22	45	10	21	1.03
Koo et al.	66	97	22	40	
Pershagen et al.	33	150	34	197	1.27

The underlined numbers are different from those assumed by Wald. We did not exclude the wives of ex-smokers.

(1) Hirayama standardized by age of women only (from Table 2, Hirayama 1984)
(2) Hirayama with age selection bias removed (Überla and Ahlborn, 1987)

Results

Meta-Analyses for All Possible Case-Control Study Combinations

In order to get a feeling for the consequences of random selection of studies, we first considered all possible combinations of case-control studies. With 10 case-control studies there are 1,023 possible study combinations or subsets for which a meta-analysis can be performed. We calculated them all. The results can be summarized as follows:

34.5% of all possible meta-analyses – using the Yusuf technique – are technically significant at $p \leqq 0.05$. That means that a random selection of studies leads to a probability of 65.5% for a negative result of the meta-analysis.

The Trichopoulos study is involved in 330 of the 353 significant study combinations, that is in 93.5%. This study is the dominant study in the significant combinations. Without the Trichopoulos study only 23 out of the 511 then possible study combinations are "significant", that is 4.5%. One has a probability of 95.5% for a negative result selecting a subset of studies for a meta-analysis randomly.

The Trichopoulos study was judged as methodologically unacceptable. It is a textbook example of how a case-control study should not be performed [29]. If it were included, however, the impact of this study on the results would prove to be heavy.

Table 3. Results of meta-analyses I

Author		Cohort only	Case-control quality +	Case-control quality −	Cohort plus CC quality +	All
Hirayama*		×			×	×
Garfinkel		×			×	×
Chan			×		×	×
Correa				×		×
Trichopoulos				×		×
Buffler			×		×	×
Kabath			×		×	×
Garfinkel			×		×	×
Akiba				×		×
Lee				×		×
Koo			×		×	×
Pershagen			×		×	×
Fisher:	p	0.017	0.604	0.007	0.137	0.009
Yusuf:	$\widehat{RR}$	1.271	1.074	1.652	1.178	1.260
	IL 95	1.025	0.848	1.201	1.005	1.093
	IU 95	1.575	1.361	2.272	1.381	1.453
	p**	0.014	0.277	0.001	0.022	0.001

* Hirayama standardized by age of women only, RR = 1.45 as calculated from Table 2, Hirayama, 1984
** one-tailed

Table 4. Results of meta-analyses II

Author		Cohort only	Cohort plus CC quality +	All without Trichopoulos	All
Hirayama adjusted*		×	×	×	×
Garfinkel		×	×	×	×
Chan			×	×	×
Correa			–	×	×
Trichopoulos			–	–	×
Buffler			×	×	×
Kabath			×	×	×
Garfinkel			×	×	×
Akiba			–	×	×
Lee			–	×	×
Koo			×	×	×
Pershagen			×	×	×
Fisher:	p	0.105	0.336	0.158	0.028
Yusuf:	$\widehat{RR}$	1.013	1.035	1.076	1.118
	IL 95	0.848	0.941	0.941	1.273
	IU 95	1.210	1.193	1.230	1.299
	p**	0.443	0.317	0.142	0.046

* With age selection bias removed. RR = 0.902 (Überla and Ahlborn 1987)
** one-tailed

Meta-Analyses for Selected Study Groups

Meta-analyses for various combinations of cohort and case-control studies were calculated. The results are given in Table 3. For the Hirayama study a relative risk of 1.45 for the exposed versus non-exposed persons is used in all these combinations as one of the starting points. The results show that the probability using the Fisher method is always higher than the probability using the procedure as applied by Yusuf [32] or Wald [31]. This had to be expected. The other methods – Mantel-Haenzsel or for the cohort studies risk ratios – do not differ much from the Yusuf method. All the study combinations on Table 3 are significant with the exception of the reasonable quality case-control studies. These six studies have a common risk estimate of 1.07, being not statistically different from unity.

The meta-analyses for these study combinations were repeated using a relative risk of 0.90 for the Hirayama study as was calculated by Überla and Ahlborn [30]. The pooled risk estimates are very close to unity and are not statistically significant (Table 4). When one includes the Trichopoulos study, the pooled estimate for the relative risk is 1.118, approaching but not reaching statistical significance.

Discussion

To summarize, the expected overall risk of dying of lung cancer for non-smoking women married to smoking men is:

- 1.074 out of six case-control studies of reasonable quality,
- 1.013 out of two prospective studies, using the Hirayama study with the age selection bias removed as shown by Überla and Ahlborn,
- 1.035 out of two prospective studies and six case-control studies of reasonable quality,
- 1.076 out of eleven studies, with the Trichopoulos study excluded, and
- 1.118 out of all twelve studies including the Trichopoulos study.

These risk estimates are not statistically different from unity.

Thus, the overall result of various meta-analyses can be summarized as follows: Meta-analysis of 12 relevant studies (using women only and adjusting the relative risk of Hirayama for age selection bias) gives an overall estimate of relative risk of dying of lung cancer for non-smoking women married to smoking men of $\widehat{RR} = 1.076$ (Trichopoulos excluded) or $\widehat{RR} = 1.118$ (Trichopoulos included). These risk increases of about 8% or 12% are not significantly different from unity.

Our results differ widely from the results given by Wald [31]. The main reasons are different relative risk estimates for the individual studies. The papers by Hirayama and Trichopoulos were the first studies to be published on this issue. All later studies give less indicative results. Whether wives of ex-smokers should be included or not, whether the Hirayama study has to be adjusted for age selection bias and whether the Trichopoulos study is methodologically as stringent as a case-control study should be is open for discussion and will be answered differently by individual scientists. We have shown a variety of possible outcomes of meta-analyses and demonstrated the sensitivity of the results with varying assumptions.

The whole question of meta-analyses comes down to the question of the quality of the individual study. As long as there are no better studies available, meta-analyses cannot and do not add much new evidence to the question whether passive smoking is related to lung cancer.

References

1. Akiba S, Kato H, Blot WJ (1986) Passive smoking and lung cancer among Japanese women. Cancer Res 46:4894–4807
2. Chan WC, Fung SC (1982) Lung cancer in non-smokers in Hong Kong. In: Grundmann E (ed) Cancer campaigne, vol 6. Cancer epidemiology. Gustav Fischer, Stuttgart, pp 199–202
3. Correa P, Pickle LW, Trontham E, Lin Y, Haenszel W (1983) Passive smoking and lung cancer. Lancet 2:595–597
4. Correa P, Pichler LW, Trontham E, Dalager E, Haenszel W (1984) The causes of lung cancer in Louisiana. In: Mizell M, Correa P (eds) Lung cancer: causes and prevention. Chemie, Weinheim, pp 73–82
5. Dalager NA, Pickle LW, Mason ThI, et al (1986) The relation of passive smoking to lung cancer. Cancer Res 46:4808–4811
6. DerSimonian R, Laird N (1986) Meta-Analysis in Clinical Trials. Controlled Clinical Trials 7:177–188
7. Garfinkel L (1984) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J Natl Canc Inst 66:1061–1066

8. Garfinkel L, Auerbach O, Joubert L (1985) Involuntary smoking and lung cancer: a case control study. J Natl Canc Inst 75:463–469
9. Gillis CR, Hole DJ, Hawthorne VM, Boyle P (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur J Respir Dis (Suppl) 133:121–126
10. Grahame R (1978) Comparison of different trials. Rheumatol Rehabil (Suppl) 135–139
11. Hirayama T (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 282:183–185
12. Hirayama T (1983) Passive smoking and lung cancer. Consistency of association. Lancet 1:1425–1426
13. Hirayama T (1984) Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P (eds) Lung cancer: causes and prevention. Chemie, Weinheim, pp 175–195
14. Hirayama T (1984) Cancer mortality in non-smoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 13:680–890
15. Kabat GC, Wynder EL (1984) Lung cancer in nonsmokers. Cancer 53:1214–1221
16. Knoth A, Bohn H, Schmidt F (1983) Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen. Med Klin 78:66–69
17. Koo LC, Ho JHC, Saw D, Path C (1983) Active and passive smoking among female lung cancer patients and control in Hong Kong. J Exp Clin Cancer Res 4:367–375
18. Koo LC, Ho JHC, Saw D, Path C (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? J Exp Clin Cancer Res 3:277–283
19. Koo LC, Ho JHC, Lee N (1985) An analysis of some risk factors for lung cancer in Hong Kong. Int J Cancer 35:149–155
20. Lee PN (1984) Lung cancer incidence and type of cigarette smoked. In: Mizell M, Correa P (eds) Lung cancer: Causes and prevention. Chemie International, Deerfield Beach, pp 373–384
21. Lee PN, Chamberlain J, Alderson HR (1986) Relationship of passive smoking to risk of lung cancer and other smoking diseases. Br J Cancer 54:97–105
22. Miller GH (1984) Cancer, passive smoking and nonemployed and employed wives. West J Med 140:632–635
23. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers ThC (1987) Meta-analyses of randomized controlled trials. N Engl J Med 316:450–455
24. Sandler DP, Everson RB, Wilcox AJ (1984) Passive smoking in adulthood and cancer risk. Am J Epid 121:37–48
25. Sandler DP, Wilcox AJ, Everson RB (1985) Cumulative effects of lifetime passive smoking on cancer risks. Lancet 1:312–315
26. Sandler DP, Everson RB, Wilcox AJ, Browder JP (1985) Cancer risk in adulthood from early life exposure to parents smoking. Am J Publ Health 75:487–492
27. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B (1981) Lung cancer and passive smoking. Int J Cancer 27:1–4
28. Trichopoulos D, Kalandidi A, Sparros L (1983) Lung cancer and passive smoking: conclusion of Greek study. Lancet 2:677–678
29. Überla K (1987) Lung cancer from passive smoking: hypothesis or convincing evidence? Int Arch Occup Environ Health 59:421–437
30. Überla K, Ahlborn U (1987) Passive smoking and lung cancer: a reanalysis of Hirayama's data. International Conference on Indoor Air Quality. Tokyo
31. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS (1986) Does breathing other people's tobacco smoke cause lung cancer? Br Med J 293:1217–1222
32. Yusuf S, Peto R, Lewis J, Collins R, Sleight P (1985) Beta blockade during and after myocardial infarction: an overview of the randomized trials. Progress in Cardiovascular Diseases Vol XXVII 5:338

Epidemiological Issues on Involuntary Smoking and Lung Cancer

Y. Shimizu, T. Namekata, and K. Takemoto

Summary

Both case-control and cohort studies of passive smoking and lung cancer published since 1981 were reviewed with the intent to make recommendations for future epidemiologic study of this controversial topic. The relative risk of lung cancer among non-smoking women married to smoking men compared to non-smoking women married to non-smoking men varied considerably over a range from 0.75 to 3.4 dependent on sample size, histological type studied, type of questionnaire administered, case ascertainment method, country or nationality of the study population, and age of the study population [28]. Major possible sources of bias and misclassification have been considered by other investigators and committees [22, 28]. Some new observations are made on these already carefully scrutinized data and an attempt is made to give concrete solutions for solving the problems of low-level risk assessment of this indoor environmental air pollutant and its potential carcinogenic effect.

Introduction

Since the disclosure of the 1964 Surgeon General's report [29], cigarette smoking has been labeled one of the most insidious health hazards encountered by humans in the twentieth century. With the establishment of tobacco smoke as a carcinogen, the question arises: If tobacco smoke is hazardous to those who directly inhale it, then what are the possible health consequences to an individual who breathes this potential carcinogen on a second hand basis by sharing the same air space as an active smoker?

This issue has ignited a conflagration of public debate, beginning in 1981 [11], due to the involuntary nature of exposure to environmental tobacco smoke (ETS) in the workplace and at home. Scientific debate is ongoing, involving careful scrutiny of the dozen or so reports of the effects of ETS on lung cancer incidence.

An epidemiological review of the relevant papers was conducted to improve future studies of passive smoking and lung cancer and the following general observations were made:

1) The age range of subjects in some studies was inappropriate to allow for latency of the outcome of interest (lung cancer) to occur;
2) Adequate statistical power was not obtained in many studies due to small numbers of cases and controls;
3) Misclassification of the disease variable (lung cancer), of case or control eligibility (non-smokers), and of the exposure variable (smoking spouse) is not only possible but probable to some degree in all of the studies reviewed;

H. Kasuga (Ed.) Indoor Air Quality